(FILE 'HOME' ENTERED AT 15:16:28 ON 16 JUL 1998)

FILE 'MEDLINE, CAPLUS, WPIDS' ENTERED AT 15:16:38 ON 16 JUL 1998

L1	5670	S APOPTOSIS AND RECEPTOR
L2	175	S L1 AND DEATH DOMAIN
L3	107	DUP REM L2 (68 DUPLICATES REMOVED)
L4	23	S L3 AND PY>1997
L5	84	S L3 NOT L4
L6	86	S DEATH RECEPTOR
L7	55	DUP REM L6 (31 DUPLICATES REMOVED)

L2 ANSWER 1 OF 26 MEDLINE
AN 1998044290 MEDLINE
DN 98044290
TI A novel receptor for Apo2L/TRAIL contains a truncated death domain.
AU **Marsters S A**; Sheridan J P; Pitti R M; Huang A; Skubatch M; Baldwin D; Yuan J; Gurney A; Goddard A D; Godowski P; Ashkenazi A
CS Department of Molecular Oncology, Genentech Inc., 1 DNA Way, South San Francisco, California 94080-4918, USA.
SO CURRENT BIOLOGY, (1997 Dec 1) 7 (12) 1003-6.
Journal code: B44. ISSN: 0960-9822.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AF147230
EM 199804
EW 19980403
AB Apo2 ligand (Apo2L [1], also called TRAIL for tumor necrosis factor (TNF)-related apoptosis-inducing ligand [2]) belongs to the TNF family and activates apoptosis in tumor cells. Three closely related receptors bind Apo2L: DR4 and DR5, which contain cytoplasmic death domains and signal apoptosis, and DcR1, a decoy receptor that lacks a cytoplasmic tail and inhibits Apo2L function [3-5]. By cross-hybridization with DcR1, we have identified a fourth Apo2L receptor, which contains a cytoplasmic region with a truncated death domain. We subsequently named this protein decoy receptor 2 (DcR2). The DcR2 gene mapped to human chromosome 8p21, as did the genes encoding DR4, DR5 and DcR1. A single DcR2 mRNA transcript showed a unique expression pattern in human tissues and was particularly abundant in fetal liver and adult testis. Upon overexpression, DcR2 did not activate apoptosis or nuclear factor-kappaB; however, it substantially reduced cellular sensitivity to Apo2L-induced apoptosis. These results suggest that DcR2 functions as an inhibitory Apo2L receptor.

L2 ANSWER 2 OF 26 MEDLINE
AN 97390509 MEDLINE
DN 97390509
TI Control of TRAIL-induced apoptosis by a family of signaling and decoy receptors [see comments].
CM Comment in: Science 1997 Aug 8;277(5327):768
AU Sheridan J P; **Marsters S A**; Pitti R M; Gurney A; Skubatch M; Baldwin D; Ramakrishnan L; Gray C L; Baker K; Wood W I; Goddard A D; Godowski P; Ashkenazi A
CS Department of Molecular Oncology, Genentech, South San Francisco, CA 94080-4918, USA.
SO SCIENCE, (1997 Aug 8) 277 (5327) 818-21.
Journal code: UJ7. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
OS GENBANK-AF012535; GENBANK-AF012536
EM 199710
AB TRAIL (also called Apo2L) belongs to the tumor necrosis factor family, activates rapid apoptosis in tumor cells, and binds to the death-signaling receptor DR4. Two additional TRAIL receptors were identified. The receptor designated death receptor 5 (DR5) contained a cytoplasmic death domain and induced apoptosis much like DR4. The

receptor designated decoy receptor 1 (DcR1) displayed properties of a glycophospholi[redacted]-anchored cell surface protein[redacted]cR1 acted as a decoy receptor t[redacted] inhibited TRAIL signaling. Thu[redacted], a cell surface mechanism exists for the regulation of cellular responsiveness to pro-apoptotic stimuli.

L2 ANSWER 3 OF 26 MEDLINE
AN 97306297 MEDLINE
DN 97306297
TI Herpesvirus entry mediator, a member of the tumor necrosis factor receptor (TNFR) family, interacts with members of the TNFR-associated factor family and activates the transcription factors NF-kappaB and AP-1.
AU **Marsters S A**; Ayres T M; Skubatch M; Gray C L; Rothe M; Ashkenazi A
CS Department of Molecular Oncology, Genentech, Inc., South San Francisco, California 94080-4918, USA.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 May 30) 272 (22) 14029-32. Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199709
EW 19970901
AB The mammalian tumor necrosis factor receptor (TNFR) family consists of 10 cell-surface proteins that regulate development and homeostasis of the immune system. Based on an expressed sequence tag, we have cloned a cDNA encoding a novel member of the human TNFR family. A closely related protein, designated HVEM (for herpesvirus entry mediator), was identified independently by another group as a mediator of herpesvirus entry into mammalian cells (Montgomery, R., Warner, M., Lum, B., and Spear, P. (1996) Cell 87, 427-436). HVEM differed from our clone by two amino acid residues, suggesting that the two proteins represent polymorphism of a single HVEM gene. We detected HVEM mRNA expression in several human fetal and adult tissues, although the predominant sites of expression were lymphocyte-rich tissues such as adult spleen and peripheral blood leukocytes. The cytoplasmic region of HVEM bound to several members of the TNFR-associated factor (TRAF) family, namely TRAF1, TRAF2, TRAF3, and TRAF5, but not to TRAF6. Transient transfection of HVEM into human 293 cells caused marked activation of nuclear factor-kappaB (NF-kappaB), a transcriptional regulator of multiple immunomodulatory and inflammatory genes. HVEM transfection induced also marked activation of Jun N-terminal kinase, and of the Jun-containing transcription factor AP-1, a regulator of cellular stress-response genes. These results suggest that HVEM is linked via TRAFs to signal transduction pathways that activate the immune response.

L2 ANSWER 4 OF 26 MEDLINE
AN 97148200 MEDLINE
DN 97148200
TI Apo-3, a new member of the tumor necrosis factor receptor family, contains a death domain and activates apoptosis and NF-kappa B.
AU **Marsters S A**; Sheridan J P; Donahue C J; Pitti R M; Gray C L; Goddard A D; Bauer K D; Ashkenazi A
CS Department of Molecular Oncology, Genentech, Inc., South San Francisco, California 94080-4918, USA.
SO CURRENT BIOLOGY, (1996 Dec 1) 6 (12) 1669-76. Journal code: B44. ISSN: 0960-9822.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U74611

EM 199705
AB BACKGROUND: Two [redacted]eptors that contain the so-cal[redacted] "death domain' have been describ[redacted] to date: tumor necrosis factor receptor 1 (TNFR1) and Fas/Apo-1 (CD95); both belong to the TNFR gene family. The death domain of TNFR1 mediates the activation of programmed cell death (apoptosis) and of the transcription factor NF-kappa B, whereas the death domain of CD95 only appears to activate apoptosis. RESULTS: We have identified an additional member of the TNFR family, which we have named Apo-3. Apo-3 is a transmembrane protein of approximately 47 kDa that has similarity of members of the TNFR family in its extracellular, cysteine-rich domains. In addition, Apo-3 resembles TNFR1 and CD95 in that it contains a cytoplasmic death domain. The Apo-3 gene mapped to human chromosome 1p36.3, and Apo-3 mRNA was detected in several human tissues, including spleen, thymus, peripheral blood lymphocytes, small intestine and colon. Ectopic expression of Apo-3 in HEK293 or HeLa cells induced marked apoptosis. CrmA, a poxvirus inhibitor of Ced-3-like proteases which blocks death signaling by TNFR1 and CD95, inhibited Apo-3-induced apoptosis. Ectopic expression of Apo-3 also induced the activation of NF-kappa B. Apo-3 did not specifically bind to the Apo-2 ligand, suggesting the existence of a distinct ligand for Apo-3. CONCLUSIONS: These results identify Apo-3 as a third member of the TNFR family that activates apoptosis, and suggest that Apo-3, TNFR1 and CD95 engage a common apoptotic cell-death machinery. Apo-3 resembles TNFR1 because it can stimulate NF-kappa B activity and regulate apoptosis. Apo-3 mRNA is expressed in various tissues, consistent with the possibility that this receptor may regulate multiple signaling functions.

L2 ANSWER 5 OF 26 MEDLINE
AN 96385443 MEDLINE
DN 96385443
TI Activation of apoptosis by Apo-2 ligand is independent of FADD but blocked by CrmA.
AU **Marsters S A**; Pitti R M; Donahue C J; Ruppert S; Bauer K D; Ashkenazi A
CS Department of Molecular Oncology, Genantech Inc., South San Francisco, California 94080, USA.
SO CURRENT BIOLOGY, (1996 Jun 1) 6 (6) 750-2.
Journal code: B44. ISSN: 0960-9822.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199705
AB A new member of the tumor necrosis factor (TNF) cytokine family, designated Apo-2 ligand (Apo-21) [1] or TRAIL [2], has been shown recently to induce apoptosis in various tumor cell lines; however, its biological role is unknown. Here, we show that Apo-21, activated apoptosis in T-cell-enriched cultures of peripheral blood lymphocytes stimulated by interleukin-2 (IL-2), but not in unstimulated cells. This finding suggests that, like Fas/Apo-1 ligand and TNF [3-5], Apo-2L may play a role in regulating post-stimulation apoptosis of mature lymphocytes. Studies on the mechanism of Apo-2L action demonstrated marked membrane blebbing, a hallmark of apoptosis, within a few minutes of the addition of Apo-2L to tumor cells. Ectopic expression of a dominant negative mutant of FADD, a cytoplasmic protein that mediates death signalling by Fas/Apo-1 and by TNF receptor type 1 (TNFR1) [6-9], inhibited the induction of apoptosis by anti-Fas/Apo-1 antibody, but had little effect on Apo-2L function. In contrast, expression of CrmA, a cowpox virus-derived inhibitor of the Ced-2-like proteases ICE [10] and CPP32/Yama [11,12], blocked the induction of apoptosis by either Apo-2L or anti-Fas/Apo-1 antibody. These results suggest that Apo-2L activates a rapid, FADD-independent pathway to trigger a cell-death programme that requires the function of cysteine proteases such as

ICE or CPP32/Yama.

L2 ANSWER 6 OF 26 MEDLINE
AN 96278649 MEDLINE
DN 96278649
TI Induction of apoptosis by Apo-2 ligand, a new member of the tumor necrosis factor cytokine family.
AU Pitti R M; **Marsters S A**; Ruppert S; Donahue C J; Moore A; Ashkenazi A
CS Department of Molecular Oncology, Genentech, Inc., South San Francisco, California 94080-4990, USA.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 May 31) 271 (22) 12687-90. Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
EM 199610
AB Cytokines in the tumor necrosis factor (TNF) family regulate development and function of the immune system. We have isolated a new member of this family, designated Apo-2 ligand (Apo-2L), via an expressed sequence tag. Apo-2L is a 281-amino acid protein, related most closely to Fas/Apo-1 ligand. Transfected Apo-2L is expressed at the cell surface with its C terminus exposed, indicating a type II transmembrane protein topology. Like Fas/Apo-1 ligand and TNF, the C-terminal extracellular region of Apo-2L (amino acids 114-281) exhibits a homotrimeric subunit structure. Soluble Apo-2L induces extensive apoptosis in lymphoid as well as non-lymphoid tumor cell lines. The effect of Apo-2L is not inhibited by soluble Fas/Apo-1 and TNF receptors; moreover, expression of human Fas/Apo-1 in mouse fibroblasts, which confers sensitivity to induction of apoptosis by agonistic anti-Fas/Apo-1 antibody, does not confer sensitivity to Apo-2L. Hence, Apo-2L acts via a receptor which is distinct from Fas/Apo-1 and TNF receptors. These results suggest that, along with other family members such as Fas/Apo-1 ligand and TNF, Apo-2L may serve as an extracellular signal that triggers programmed cell death.

L2 ANSWER 7 OF 26 MEDLINE
AN 96220508 MEDLINE
DN 96220508
TI Ligand-induced assembly and activation of the gamma interferon receptor in intact cells.
AU Bach E A; Tanner J W; **Marsters S**; Ashkenazi A; Aguet M; Shaw A S; Schreiber R D
CS Department of Pathology, Washington University School of Medicine St. Louis, Missouri 63110, USA.
NC CA43059 (NCI)
SO MOLECULAR AND CELLULAR BIOLOGY, (1996 Jun) 16 (6) 3214-21. Journal code: NGY. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199609
AB Functionally active gamma interferon (IFN-gamma) receptors consist of an alpha subunit required for ligand binding and signal transduction and a beta subunit required primarily for signaling. Although the receptor alpha chain has been well characterized, little is known about the specific role of the receptor beta chain in IFN-gamma signaling. Expression of the wild-type human IFN-gamma receptor beta chain in murine L cells that stably express the human IFN-gamma receptor alpha chain (L.hgR) produced a murine cell line (L.hgR.myc beta) that responded to human IFN-gamma. Mutagenesis of the receptor beta-chain intracellular domain revealed that only two closely spaced, membrane-proximal sequences (P263PSIP267 and

I270EEYL274) are required for function. Coprecipitation studies showed that these sequences are necessary for the specific and constitutive association of the receptor beta chain with the JAK-2 tyrosine kinase. These experiments also revealed that the IFN-gamma receptor alpha and beta chains are not preassociated on the surface of unstimulated cells but rather are induced to associate in an IFN-gamma-dependent fashion. A chimeric protein in which the intracellular domain of the beta chain was replaced by JAK-2 complemented human IFN-gamma signaling and biologic responsiveness in L.hgR. In contrast, a c-src-containing beta-chain chimera did not. These results indicate that the sole obligate role of the IFN-gamma receptor beta chain in signaling is to recruit JAK-2 into the ligand-assembled receptor complex.

AN 97148200 MEDLINE
DN 97148200
TI **Apo-3**, a new member of the tumor necrosis factor receptor family, contains a **death domain** and activates apoptosis and NF-kappa B.
AU Marsters S A; Sheridan J P; Donahue C J; Pitti R M; Gray C L; Goddard A D; Bauer K D; Ashkenazi A
CS Department of Molecular Oncology, Genentech, Inc., South San Francisco, California 94080-4918, USA.
SO CURRENT BIOLOGY, (1996 Dec 1) 6 (12) 1669-76.
Journal code: B44. ISSN: 0960-9822.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U74611
EM 199705
AB BACKGROUND: Two receptors that contain the so-called "death domain' have been described to date: tumor necrosis factor receptor 1 (TNFR1) and Fas/Apo-1 (CD95); both belong to the TNFR gene family. The death domain of TNFR1 mediates the activation of programmed cell death (apoptosis) and of the transcription factor NF-kappa B, whereas the death domain of CD95 only appears to activate apoptosis. RESULTS: We have identified an additional member of the TNFR family, which we have named **Apo-3**. **Apo-3** is a transmembrane protein of approximately 47 kDa that has similarity of members of the TNFR family in its extracellular, cysteine-rich domains. In addition, **Apo-3** resembles TNFR1 and CD95 in that it contains a cytoplasmic death domain. The **Apo-3** gene mapped to human chromosome 1p36.3, and **Apo-3** mRNA was detected in several human tissues, including spleen, thymus, peripheral blood lymphocytes, small intestine and colon. Ectopic expression of **Apo-3** in HEK293 or HeLa cells induced marked apoptosis. CrmA, a poxvirus inhibitor of Ced-3-like proteases which blocks death signaling by TNFR1 and CD95, inhibited **Apo-3**-induced apoptosis. Ectopic expression of **Apo-3** also induced the activation of NF-kappa B. **Apo-3** did not specifically bind to the Apo-2 ligand, suggesting the existence of a distinct ligand for **Apo-3**. CONCLUSIONS: These results identify **Apo-3** as a third member of the TNFR family that activates apoptosis, and suggest that **Apo-3**, TNFR1 and CD95 engage a common apoptotic cell-death machinery. **Apo-3** resembles TNFR1 because it can stimulate NF-kappa B activity and regulate apoptosis. **Apo-3** mRNA is expressed in various tissues, consistent with the possibility that this receptor may regulate multiple signaling functions.

(FILE 'USPAT' ENTERED AT 15:09:34 ON 16 JUL 1998)

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L1          418 S APOPTOSIS
L2         2289 S CELL DEATH
L3            0 S CELL DEATH DOMAIN
L4            4 S DEATH DOMAIN
L5          273 S (L1 OR L2)(P)RECEPTOR
L6            2 S DEATH DOMAIN(3A)RECEPTOR
L7           13 S L1(3A)RECEPTOR
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=> d l4 1- bib ab

US PAT NO: 5,712,381 [IMAGE AVAILABLE] L4: 1 of 4
DATE ISSUED: Jan. 27, 1998
TITLE: MADD, a TNF receptor **death domain** ligand protein
INVENTOR: Lih-Ling Lin, Concord, MA
Jennifer Chen, Chestnut Hill, MA
Andrea R. Schievella, Winchester, MA
James Graham, Somerville, MA
ASSIGNEE: Genetics Institute, Inc., Cambridge, MA (U.S. corp.)
APPL-NO: 08/698,551
DATE FILED: Aug. 15, 1996
ART-UNIT: 182
PRIM-EXMR: Stephen Walsh
ASST-EXMR: Mukul Ranjan
LEGAL-REP: Scott A. Brown, Suzanne A. Sprunger, Thomas J. DesRosier

US PAT NO: 5,712,381 [IMAGE AVAILABLE] L4: 1 of 4

ABSTRACT:
Novel TNF receptor **death domain** ("TNF-R1-DD") ligand proteins are disclosed. Polynucleotides encoding the TNF-R1-DD ligand protein are also disclosed, along with vectors, host cells, and methods of making the TNF-R1-DD ligand protein. Pharmaceutical compositions containing the TNF-R1-DD ligand protein, methods of treating inflammatory conditions, and methods of inhibiting TNF-R **death domain** binding are also disclosed. Methods of identifying inhibitors of TNF-R **death domain** binding and inhibitors identified by such methods are also disclosed.

US PAT NO: 5,712,115 [IMAGE AVAILABLE] L4: 2 of 4
DATE ISSUED: Jan. 27, 1998
TITLE: Human cell death-associated protein
INVENTOR: Phillip R. Hawkins, Mountain View, CA
Scott Michael Braxton, San Mateo, CA
Lynn E. Murry, Portola Valley, CA
ASSIGNEE: Incyte Pharmaceuticals, Inc., Palo Alto, CA (U.S. corp.)
APPL-NO: 08/618,164
DATE FILED: Mar. 19, 1996
ART-UNIT: 186
PRIM-EXMR: Christina Y. Chan
ASST-EXMR: Emma Cech
LEGAL-REP: Lucy J. Billings, Barbara J. Luther

US PAT NO: 5,712,115 [IMAGE AVAILABLE] L4: 2 of 4

ABSTRACT:
The present invention provides a polynucleotide which identifies and encodes a human cell death-associated protein (cdap) which was isolated from a rheumatoid synovium library. The invention provides for genetically engineered expression vectors and host cells comprising a nucleic acid sequence encoding CDAP. The invention also provides for the therapeutic use of purified CDAP, cdap or its antisense molecules, or CDAP inhibitors in pharmaceutical compositions and for treatment of conditions or diseases associated with expression of CDAP. The invention also describes diagnostic assays which utilize diagnostic compositions comprising the polynucleotide, or fragments thereof, or antibodies which specifically bind to the polypeptide.

US PAT NO: 5,674,734 [IMAGE AVAILABLE] L4: 3 of 4
DATE ISSUED: Oct. 7, 1997
TITLE: Cell death protein
INVENTOR: Philip Leder, Chestnut Hill, MA
Brian Seed, Boston, MA
Ben Z. Stanger, Brookline, MA
Tae-Ho Lee, Daejeon, Republic of Korea
Emily Kim, Chestnut Hill, MA
ASSIGNEE: President and Fellows of Harvard College, Cambridge, MA (U.S. corp.)
The General Hospital Corporation, Boston, MA (U.S. corp.)
APPL-NO: 08/444,005
DATE FILED: May 18, 1995
ART-UNIT: 184
PRIM-EXMR: Robert A. Wax
ASST-EXMR: Tekchand Saidha
LEGAL-REP: Clark & Elbing LLP

US PAT NO: 5,674,734 [IMAGE AVAILABLE] L4: 3 of 4

ABSTRACT:
Disclosed is a protein, designated RIP, which contains a **death domain** at its carboxy terminus and a kinase domain at its amino terminus. RIP interacts with the Fas/APO-1 intracellular domain and the TNFR1 intracellular domain. When expressed in transformed host cells, recombinant RIP promotes apoptosis. Also disclosed are DNA molecules encoding RIP, anti-RIP antibodies, and screening methods for discovering inhibitors of RIP-dependent apoptosis.

US PAT NO: 5,563,039 [IMAGE AVAILABLE] L4: 4 of 4
DATE ISSUED: Oct. 8, 1996
TITLE: TNF receptor-associated intracellular signaling proteins and methods of use
INVENTOR: David V. Goeddel, South San Francisco, CA
Hailing Hsu, South San Francisco, CA
ASSIGNEE: Tularik, Inc., So. San Francisco, CA (U.S. corp.)
APPL-NO: 08/414,625
DATE FILED: Mar. 31, 1995
ART-UNIT: 182
PRIM-EXMR: John Ulm
LEGAL-REP: Flehr, Hohbach, Test, Albritton & Herbert

US PAT NO: 5,563,039 [IMAGE AVAILABLE] L4: 4 of 4

ABSTRACT:
A novel family of intracellular signaling proteins, exemplified by a Tumor Necrosis Factor Receptor-1 Associated **Death Domain** protein (TRADD), share a common TRADD sequence and include transducers of signals that modulate cell growth, differentiation and apoptosis. As such, the TRADD proteins, TRADD-encoding nucleic acids, and natural TRADD intracellular binding targets provide both important targets and means

for therapeutic intervention. In particular, the invention provides isolated TRADDs and TRA[redacted] fragments, nucleic acids encod[redacted] the subject TRADDs and TRADD fragme[redacted]s or capable of selectively hyb[redacted]dizing to such TRADD-encoding nucleic acids, vectors and cells comprising TRADD-encoding nucleic acids, and TRADD-specific binding reagents. These compositions find use in diagnostic and therapeutic methods for disease associated with undesirable cell growth, migration, differentiation and/or cytokine signal responsiveness and methods and compositions for identifying lead compounds and pharmacological agents.